How can we stabilize QT variability?

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Many variables of the QT interval have been used for the risk stratification of various cardiovascular diseases. The QT interval represents the repolarization phase of the ventricles and this phase is important for the process of EC coupling of the myocardium. Changes in electrophysiological balance in the repolarization phase have the potential for both antiarrhythmic and proarrhythmic effects. Initially, QT interval abnormality (that is, QT prolongation) was recognized in children with sudden death. Almost 60 years passed after the recognition of the first long QT syndrome cases, and the QT interval is still the most important clinical characteristic and predictor of prognosis in patients with long QT syndrome[1]. QT prolongation has also been applied for prediction of various cardiovascular diseases and prolonged QT interval has been linked to an increased risk of cardiovascular death[2].

The QT segment is not stable. Since the QT interval is influenced by previous RR interval or diastolic interval (interval between the end of T wave of the previous beat and the onset of R wave of the present beat), variability of the QT segment is strongly associated with variability of the previous RR intervals. Moreover, the QT interval also depends on a much longer history of the previous RR intervals 2-3 min before the present beats (QT hysteresis). Although some indices of QT variability have been proposed to reduce the influence of RR variance on the QT interval, detection of microvolt T-wave alternans (MTWA)[3] is a most popular method to detect repolarization instability. MTWA can detect electrical instability as the presence of T-wave amplitude at a 0.5 cycle-per-beat periodicity and requires a stress test to increase the heart rate for

induction of the MTWA. Although a few studies failed to show the predictive value of the MTWA[4, 5], most of the studies and meta-analysis found the positive MTWA as a risk factor for sudden cardiac death in patients with heart failure[6, 7]. The QT variability index (QTVI) is an alternative method to detect beat-to-beat changes in the repolarization duration, adjusting the measurement for heart rate variance[8]. Usually 5 to 10 minutes-ECG recording at rest is available to analyze the QTVI and it also can detect both alternate and non-alternate QT oscillations. The magnitude of alternate and non-alternate T wave oscillations increased immediately before the onset of ventricular tachyarrhythimia[9] and the QTVI is a useful method to identify unstable repolarization variability that MTWA fails to detect. Previous studies showed patients with ischemic or non-ischemic dilated cardiomyopathy had increased QTVI compared to control subjects[8, 10, 11]. The value of QTVI depended on severity of New York Heart Association (NYHA) functional class and was a predictor of total mortality, sudden cardiac death, and occurrence of ventricular tachyarrhythmias. The QTVI did not correlate with heart rate variability, which usually is reduced in heart failure.

In this issue of the Journal, Dobson et al[12] reported that QTVI was associated with increased risk for total and cardiovascular mortality in patients with heart failure from the GISSI-HF trial. Since the QTVI had circadian variation that was the lowest in the midnight to early morning hours and increased throughout the day[13], authors used data from the 24-hour Holter ECG recording and found QTVI at high heart rate did not have predictable value but the QTVI at low heart rate had significant results. The present and previous studies indicate that increased QTVI is associated with poor

prognosis in patients with heart failure.

One can ask why the increased variability of QT interval is not good for patients with heart failure. The answer is that abnormal QT interval variability represents the results of electrical remodeling in the failing heart. Reduced cardiac output in the failing heart promotes sympathetic neurohumoral activation and electrophysiological changes in the failing myocardium[14] to increase cardiac output and maintain systemic perfusion, but these compensatory responses also have arrhythmogenic effects. Electrophysiological changes in the failing myocyte result in prolongation of the action potential duration to enhance intracellular Ca^{2+} handling and cardiac contractility. The outward K^+ currents are downregulated[15] in failing hearts by alteration of the channel kinetics or reduced expression of the channel proteins. Alterations in intracellular Ca^{2+} handling in the failing myocyte cause prolongation of the Ca^{2+} transient and intracellular Ca^{2+} overload. Increased Na^+/Ca^{2+} exchanger activity attempts to reduce Ca^{2+} overload but it causes inward depolarizing current and promotes triggered activity through early and delayed afterdepolarizations[14]. Conduction disturbances occur from myocardial fibrosis or downregulation of connexin and can be a substrate for reentrant ventricular arrhythmias. Oscillation of the action potential is associated with the alternation of overloading in the Ca^{2+} transient cascade and initiation of afterdepolarizations, all enhanced by increased sympathetic nervous activity. Experimentally, transient activation of the sympathetic nerve increases QT variability and induces arrhythmias in the canine model of the pacing-induced heart failure[16].

If QT variability represents unstable repolarization, how can we stabilize QT variability? Because QTVI is associated with severity of NYHA functional class, treatment of heart failure could stabilize QT oscillations. Since adrenergic stimulation enhances the occurrence of QT variability, adequate beta-blocker therapy reduces the QTVI[17]. Although both metoprolol and carvedilol improved the QTVI in patients with heart failure, the effect of carvedilol on stabilization of the QTVI was superior than metoprolol[17]. Stabilization of QT variability can be one of the mechanisms of reduction of sudden death or ventricular tachyarrhythmia by beta-blocker in patients with heart failure. Although class III antiarrhythmic drugs seem not to influence on the QTVI at therapeutic doses[18], QT variability increases under conditions of drug-induced long QT syndrome with torsades de pointes[19].

In this issue of the Journal from the GISSI-HF trial, Dobson et al[12] did not mention therapeutic effects on the QTVI. The original GISSI-HF trial reported that ω-3 polyunsaturated fatty acid (PUFA) from fish oil reduced cardiovascular mortality in patients with heart failure[20] and a substudy supported the antiarrhythmic effects of the PUFA[21]. Antiarrhythmic effects of ω-3 PUFA are still controversial but PUFA can modulate electrophysiological properties of cardiac myocytes. Experimental studies showed that ω-3 PUFA reduces Ca^{2+} overload and aftertransients, and normalization of Ca^{2+} handling prevents occurrence of delayed afterdepolarizations and triggered activity in failing myocytes[22, 23]. Moreover ω-3 PUFA reduces L-type Ca^{2+} and Na^{+}/Ca^{2+} exchanger currents, and enhances the slow component of the delayed rectifier K^{+} current. These electrophysiological effects of ω-3 PUFA may reduce repolarization

oscillation and the QTVI. Future studies should explore the effects of fish oil on the QTVI in the patients with heart failure.

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